

## **REMARKS/ARGUMENTS**

In the Examiner's March 10, 2006 Office Action, the Examiner rejected claims 31, 33, 40 and 48-50 pending in the application. This response amends claims 31, 33, 48 and 49 for consideration. After entry of the foregoing amendments, claims 31, 33, 40 and 48-50 (2 independent claims; 6 total claims) remain pending in the application. Reconsideration is respectfully requested.

Applicants acknowledge the Examiner's provisional obviousness-type double patenting rejection based on copending Application No. 09/808,314. However, in that the claims in the current application have been amended and in that no claims have yet been allowed in pending Application No. 09/808,314, Applicants have not addressed the obviousness-type double patenting rejection at this time.

Applicants acknowledge the Examiner's withdrawal of the rejection of claims 31, 33, 40 and 48-50 under 35 U.S.C. §112, second paragraph, in view of the amendments previously made to the claims. Applicants also acknowledge the Examiner's withdrawal of the rejection of claims 31, 33, and 40 under 35 U.S.C. §102(b) as being anticipated by Gaskell and Brownsey, Gaskell, Bonfanti or Davoli in view of the amendments previously made to the claims. Applicants also acknowledge the Examiner's withdrawal of the rejection of claims 31, 33, 40, and 48-50 under 35 U.S.C. §102(b) as being anticipated by Lisek in view of the amendments previously made to the claims.

### **New Grounds of Rejection**

The Examiner first rejected claims 31, 33, 40 and 48-50 under 35 U.S.C. §103(a) as being unpatentable over Duncan (Duncan, M.W. et al., Rapid Communications in Mass Spectrometry, 7:1090-1094, 1993) in view of Nuwaysir (Nuwaysir, L.M. et al. J. Am. Soc. Mass Spectrom., 4:662-669, 1993). In particular, the Examiner states that Duncan teaches the use of internal standards where the internal standards may be isotopically labeled analogues of an analyte (which falls within applicants' claim limitation of "modified analyte with shifted molecular weight") to overcome the difficulties of using MALDI for quantitative analysis of analytes. The Examiner further stated that Duncan also teaches that "real" samples require prior clean-up by, for example, immunoaffinity separation or chromatography. Further, although the Examiner conceded that Duncan fails to demonstrate the method with real samples using any type of

affinity reagent, the Examiner points out that Nuwaysir teaches a method of using metal-ion affinity chromatography to purify samples before they are analyzed by MALDI. Accordingly, the Examiner contends that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Duncan on the use of isotopically labeled internal reference standards for quantification with MALDI with those of Nuwaysir on the use of affinity chromatography for the purification of samples prior to MALDI. The Examiner further states that motivation to combine the teachings is provided by Duncan, which demonstrates the advantages of using internal standards when one wants to quantify an analyte, and Nuwaysir, which teaches that prior purification of samples with affinity chromatography is necessary for mass spectrometry of samples with a large number of peptides. Applicants respectfully traverse this rejection.

Applicants have amended their claims by further limiting the claim language to show that quantification of the analyte is done by capturing the analyte and an internal reference species (IRS) with an affinity reagent, releasing the analyte and IRS from the affinity reagent, and then analyzing and quantifying the analyte using matrix-assisted laser desorption/ionization (MALDI) on the released analyte and IRS. The sample does not undergo any additional prior clean-up or purification such as affinity chromatography as disclosed in Nuwaysir. Accordingly, since neither Duncan nor Nuwaysir, either alone or in combination, disclose Applicants' discrete steps for quantifying an analyte in a specimen, then Applicants' claimed method cannot be obvious in light of Duncan and Nuwaysir.

The Examiner has also rejected claims 31, 33, 40, 48, 49 and 50 under 35 U.S.C. §103(a) as being unpatentable over Duncan in view of Hutchens, U.S. Patent No. 6,528,320 (hereafter "Hutchens"). In particular, the Examiner states that Duncan teaches the use of internal standards where the internal standards may be isotopically labeled analogues of an analyte (which falls within applicants' claim limitation of "modified analyte with shifted molecular weight") to overcome the difficulties of using MALDI for quantitative analysis of analytes. The Examiner further stated that Duncan also teaches that "real" samples require prior clean-up by, for example, immunoaffinity separation or chromatography. Further, although the Examiner conceded that Duncan fails to demonstrate the method with real samples using any type of affinity reagent, the Examiner points out that Hutchens teaches a method of capturing an analyte from a sample on a sample presenting surface derivatized with an affinity reagent that binds the analyte, wherein the affinity reagent is a metal ion, a protein, a peptide, a nucleic acid or a dye,

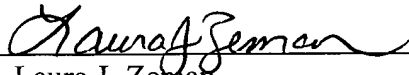
followed by detecting the captured analyte by laser desorption/ionization mass spectrometry. Therefore, the Examiners contends that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Duncan on the use of isotope-labeled internal standards for quantification with MALDI with those of Hutchens on the use of affinity reagents for the purification of samples prior to MALDI. The Examiner further states that the motivation to combine the teachings is provided by Duncan, which demonstrates the advantages of using internal standards when one wants to quantify an analyte, and by Hutchens, which teaches that prior purification of samples with an affinity reagent is necessary for mass spectrometry of samples. Applicants respectfully traverse this rejection.

Hutchens et al. discloses a mass spectrometer probe or other sample presenting surface and a method of using the probe or surface for desorption and ionization of analytes. The probe or presenting surface includes a layer of energy absorbing molecules and/or affinity directed analyte capture devices on its surface that are free of analyte and analyte is then applied to the probe or presenting surface. The analyte can be desorbed by a high energy source and detected in the mass spectrometer. Clearly, Hutchens et al. teaches putting media and captured analyte onto a probe tip or presenting surface and then conducting mass spectrometry. In contrast, Applicants sample on which mass spectrometry is conducted does not include an affinity reagent. Instead, Applicants' claims are directed to capturing an analyte species and an internal reference species (IRS) with an affinity reagent, releasing the isolated analyte species and IRS from the affinity reagent, and then detecting the presence of the isolated and released analyte species and IRS using mass spectrometry. Accordingly, since neither Duncan nor Hutchens, either alone or in combination, disclose Applicants' discrete steps for quantifying an analyte in a specimen, then Applicants' claimed method cannot be obvious in light of Duncan and Hutchens.

Further, in that Applicants' most recent claim amendments were directed to excessively limiting the scope of Applicants' method claims, and in that Applicants' previous amendments and responses contained limitations and language which made it clear with respect to what Applicants were trying to claim, Applicants contend that the most recently proposed amendments do not raise any new issues that would require further consideration and/or search. Moreover, Applicants contend that the amendments filed just prior to the issuance of the Examiner's final rejection did not necessitate the Examiner's new grounds of rejection that were issued in the Examiner's final office action.

In view of the foregoing, Applicants respectfully submit that all of the pending claims fully comply with 35 U.S.C. §112 and are allowable over the prior art of record. Reconsideration of the application and allowance of all pending claims is earnestly solicited. Should the Examiner wish to discuss any of the above in greater detail or deem that further amendments should be made to improve the form of the claims, then the Examiner is invited to telephone the undersigned at the Examiner's convenience.

Respectfully submitted,

By:   
Laura J. Zeman  
Reg. No. 36,078

**SNELL & WILMER L.L.P.**  
One Arizona Center  
400 East Van Buren  
Phoenix, Arizona 85004-2202  
Telephone: (602) 382-6377  
Facsimile: (602) 382-6070